Cystic Fibrosis Agents (Alyftrek, Kalydeco, Orkambi, Symdeko, and Trikafta)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Cystic Fibrosis Agent Policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies for Alyftrek (vanzacaftor/tezacaftor/deutivacaftor), Kalydeco (ivacaftor), Orkambi (ivacaftor/lumacaftor), Symdeko (tezacaftor/ivacaftor) and Trikafta (elexacaftor/tezacaftor/ivacaftor).

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Alyftrek

Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one indicated mutation.

Kalydeco

Kalydeco (ivacaftor) is *CFTR* potentiator indicated for the treatment of CF in patients aged 1 month and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Orkambi
Orkambi (lumacaftor/ivacaftor) is approved by the FDA for the treatment of CF in patients aged 1 year and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene.

Limitation of use: The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the *F508del* mutation.

Symdeko
Symdeko (tezacaftor/ivacaftor) is indicated for the treatment of patients with CF aged 6 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the *CFTR* gene that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

Trikafta
Trikafta (elexacaftor/tezacaftor/ivacaftor) is indicated for the treatment of CF in patients aged 2 years and older who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* data.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation or a mutation that is responsive based on in vitro data.

POLICY

Required Documentation
Submission of the following information is necessary to initiate the prior authorization review:
- Genetic testing report confirming the presence of the appropriate *CFTR* gene mutation
- Submission of medical records (e.g., chart notes, laboratory values, pulmonary function tests, CFQ-R score) documenting clinical benefit from therapy

Prescriber Specialties
Medication must be prescribed by or in consultation with a pulmonologist.

Criteria for Initial Approval
A. Alyftrek (vanzacaftor/tezacaftor/deutivacaftor) may be considered **medically necessary** for the treatment of cystic fibrosis when **all** of the following criteria are met:
- Genetic testing was conducted to detect a mutation in the *CFTR* gene
- The member has one of the mutations in the *CTFR* gene listed in Appendix A
- The member is at least 6 years of age
- Alyftrek will not be used in combination with Kalydeco, Orkambi, Symdeko, or Trikafta

Initial approval will be for **6 months.**

B. **Kalydeco** (ivacaftor) may be considered **medically necessary** for the treatment of cystic fibrosis when **all** of the following criteria are met:

- Genetic testing was conducted to detect a mutation in the *CFTR* gene.
- The member has one of the mutations in the *CFTR* gene listed Appendix B
- The member is at least 1 month of age
- Kalydeco will not be used in combination with Alyftrek, Orkambi, Symdeko or Trikafta

Initial approval will be for **6 months.**

C. **Orkambi** (lumacaftor/ivacaftor) may be considered **medically necessary** for the treatment of cystic fibrosis when **all** of the following criteria are met:

- The member is at least 1 year of age
- Genetic testing was conducted to detect a mutation in the *CFTR* gene
- The member is positive for the *F508del* mutation on both alleles of the *CFTR* gene
- Orkambi will not be used in combination with Alyftrek, Kalydeco, Symdeko or Trikafta

Initial approval will be for **6 months.**

D. **Symdeko** (tezacaftor/ivacaftor) may be considered **medically necessary** for the treatment of cystic fibrosis when **all** of the following criteria are met:

- Genetic testing was conducted to detect a mutation in the *CFTR* gene.
- The member has one of the mutations in the *CFTR* gene listed in Appendix C, or the member is homozygous for the F508del mutation.
- The member is at least 6 years of age.
- Symdeko will not be used in combination with Alyftrek, Kalydeco, Orkambi or Trikafta

Initial approval will be for **6 months.**

E. **Trikafta** (elexacaftor/tezacaftor/ivacaftor) may be considered **medically necessary** for the treatment of cystic fibrosis when **all** of the following criteria are met:

- The member is at least 2 years of age
- Genetic testing was conducted to detect a mutation in the *CFTR* gene
- The member has at least one mutation of the *CFTR* gene listed in Appendix D
- Trikafta will not be used in combination with Alyftrek, Kalydeco, Orkambi, or Symdeko.

Initial approval will be for **6 months.**

Continuation of Therapy

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria and achieve a clinically meaningful response as demonstrated by any of the following:

A. Improvement in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline
B. Increased body mass index (BMI)
C. Decreased pulmonary exacerbations
D. Improvement in quality of life from baseline as demonstrated by Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score

Approval will be for **12 months**.

Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) are considered **not medically necessary** for patients who do not meet the criteria set forth above.

Quantity Limits Apply:

- Alyftrek (4mg/20mg/50mg) 84 tablets/28 days
- Alyftrek (10mg/50mg/125mg) 56 tablets/28 days
- Kalydeco 56 tablets/28 days
- Kalydeco Pak 56 packets/28 days
- Orkambi tablets 112 tablets/28 days
- Orkambi granules 56 packets/28 days
- Symdeko 56 tablets/28 days
- Trikafta 84 tablets/28 days
- Trikafta granules 56 packets/28 days

Dosing and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Appendices

Appendix A: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to Alyftrek (Alyftrek package insert)

Appendix A: List of *CFTR* Gene Mutations that are Responsive to Alyftrek					
1341G→A	D513G	G424S	L1011S	Q552P	S1159F
1507_1515del9	D565G	G463V	L102R	Q98R	S1159P
1898+3A→G	D579G	G480C	L1065P	R1048G	S1235R
2183A→G	D614G	G480S	L1077P	R1066C	S1251N
2183A→G	D836Y	G551A	L1324P	R1066H*	S1255P
2752-26A→G	D924N	G551D*	L1335P	R1066L	S13F
2789+2insA	D979V	G551S	L137P	R1066M	S341P
2789+5G→A	D993Y	G576A	L1480P	R1070Q	S364P
296+28A→G	E116K	G576A;R668C	L15P	R1070W	S492F
3041-15T→G	E116Q	G622D	L165S	R1162L	S549I
3141del9	E193K	G628R	L206W	R117C	S549N
3195del6	E292K	G85E	L320V	R117C;G576A;R668C	S549R
3199del6	E403D	G91R	L333F	R117G	S589N
3272-26A→G	E474K	G970D	L333H	R117H	S737F
3600G→A	E56K	G970S	L346P	R117L	S912L
3849+4A→G	E588V	H1054D	L441P	R117P	S945L
3849+40A→G	E60K	H1085P	L453S	R1283M	S977F
3849+10kbC→T	E822K	H1085R	L619S	R1283S	T1036N
3850-3T→G	E831X	H1375P	L967S	R170H	T1053I
4005+2T→C	E92K	H139R	L997F	R258G	T1086I
546insCTA	F1016S	H199R	M1101K	R297Q	T1246I
5T;TG12	F1052V	H199Y	M1101R	R31C	T1299I
5T;TG13	F1074L	H609R	M1137V	R31L	T338I

621+3A→G	F1099L	H620P	M150K	R334L	T351I
711+3A→G	F1107L	H620Q	M152V	R334Q	T604I
A1006E	F191V	H939R	M265R	R347H	V1153E
A1067P	F200I	H939R;H949L	M952I	R347L	V1240G
A1067T	F311del	I1027T	M952T	R347P	V1293G
A107G	F311L	I105N	N1088D	R352Q	V201M
A120T	F508C	I1139V	N1303I	R352W	V232D
A234D	F508C;S1251N	I1234Vdel6aa	N1303K	R516G	V392G
A309D	F508del	I125T	N186K	R516S	V456A
A349V	F575Y	I1269N	N187K	R553Q	V456F
A455E	F587I	I1366N	N418S	R555G	V520F
A46D	G1047R	I1398S	P140S	R560S	V562I
A554E	G1061R	I148N	P205S	R560T	V603F
A559T	G1069R	I148T	P499A	R668C	V754M
A559V	G1123R	I175V	P574H	R709Q	W1098C
A561E	G1244E	I331N	P5L	R74Q	W1282R
A613T	G1247R	I336K	P67L	R74W	W361R
A62P	G1249R	I502T	P750L	R74W;D1270N	Y1014C
A72D	G126D	I506L	P99L	R74W;V201M	Y1032C
C491R	G1349D	I506T	Q1100P	R74W;V201M;D1270N	Y109N
D110E	G149R	I556V	Q1291R	R751L	Y161D
D110H	G178E	I601F	Q1313K	R75L	Y161S
D1152H	G178R	I618T	Q237E	R75Q	Y301C
D1270N	G194R	I807M	Q237H	R792G	Y563N
D1445N	G194V	I980K	Q359R	R933G	Y569C
D192G	G27E	K1060T	Q372H	S1045Y	Y913C
D443Y	G27R	K162E	Q452P	S108F	
D443Y;G576A;R668C	G314E	K464E	Q493R	S1118F	

Appendix B: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to Kalydeco (Kalydeco package insert)

Appendix B: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to Kalydeco				
711 + 3A → G	F311del	I148T	R75Q	S589N
2789 + 5G → A	F311L	I175V	R117C	S737F
3272-26A → G	F508C	I807M	R117G	S945L
3849 + 10kbC → T	F508C;S1251N	I1027T	R117H	S977F
A120T	F1052V	I1139V	R117L	S1159F
A234D	F1074L	K1060T	R117P	S1159P
A349V	G178E	L206W	R170H	S1251N
A455E	G178R	L320V	R347H	S1255P
A1067T	G194R	L967S	R347L	T338I
D110E	G314E	L997F	R352Q	T1053I
D110H	G551D	L1480P	R553Q	V232D
D192G	G551S	M152V	R668C	V562I
D579G	G576A	M952I	R792G	V754M
D924N	G970D	M952T	R933G	V1293G

D1152H	G1069R	P67L	R1070Q	W1282R
D1270N	G1244E	Q237E	R1070W	Y1014C
E56K	G1249R	Q237H	R1162L	Y1032C
E193K	G1349D	Q359R	R1283M	
E822K	H939R	Q1291R	S549N	
E831X	H1375P	R74W	S549R	

Appendix C: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko (Symdeko package insert)

Appendix C: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to Symdeko					
546insCTA	E92K	G576A	L346P	R117G	S589N
711 + 3A → G	E116K	G576A;R668C	L967S	R117H	S737F
2789 + 5G → A	E193K	G622D	L997F	R117L	S912L
3272-26A → G	E403D	G970D	L1324P	R117P	S945L
3849 + 10kbC → T	E588V	G1069R	L1335P	R170H	S977F
A120T	E822K	G1244E	L1480P	R258G	S1159F
A234D	E831X	G1249R	M152V	R334L	S1159P
A349V	F191V	G1349D	M265R	R334Q	S1251N
A455E	F311del	H939R	M952I	R347H	S1255P
A554E	F311L	H1054D	M952T	R347L	T338I
A1006E	F508C	H1375P	P5L	R347P	T1036N
A1067T	F508C;S1251N	I148T	P67L	R352Q	T1053I
D110E	F508del	I175V	P205S	R352W	V201M
D110H	F575Y	I336K	Q98R	R553Q	V232D
D192G	F1016S	I601F	Q237E	R668C	V562I
D443Y	F1052V	I618T	Q237H	R751L	V754M
D443Y;G576A;R668C	F1074L	I807M	Q359R	R792G	V1153E
D579G	F1099L	I980K	Q1291R	R933G	V1240G
D614G	G126D	I1027T	R31L	R1066H	V1293G
D836Y	G178E	I1139V	R74Q	R1070Q	W1282R
D924N	G178R	I1269N	R74W	R1070W	Y109N
D979V	G194R	I1366N	R74W;D1270N	R1162L	Y161S
D1152H	G194V	K1060T	R74W;V201M	R1283M	Y1014C
D1270N	G314E	L15P	R74W;V201M;D1270N	R1283S	Y1032C
E56K	G551D	L206W	R75Q	S549N	
E60K	G551S	L320V	R117C	S549R	

Appendix D: List of *CFTR* Gene Mutations that are Responsive to Trikafta (Trikafta package insert)

Appendix D: List of *CFTR* Gene Mutations that are Responsive to Trikafta					
1341G-->A	D836Y	G424S	L1011S	Q98R	S118F
1507_1515del9	D924N	G463V	L1077P	R1048G	S1235R
1898+3A-->G	D979V	G480C	L1324P	R1066H	S1251N
2183A-->G	D993Y	G480S	L1335P	R1070Q	S1255P
2752-26A-->G	E116K	G551A	L137P	R1070W	S13F
2789+2insA	E116Q	G551D	L1480P	R1162L	S341P
2789+5G-->A	E193K	G551S	L15P	R117C	S364P
296+28A-->G	E292K	G576A	L165S	R117C	S492F

3041-15T-->G	E403D	G576A;R668C	L206W	R117C; G576A;R668C	S549I
3141del9	E474K	G622D	L320V	R117G	S549N
3272-26A-->G	E56K	G628R	L333F	R117H	S549R
3600G-->A	E588V	G85E	L333H	R117L	S589N
3849+10kbC-->T	E60K	G85E	L346P	R117P	S737F
3849+4A-->G	E822K	G907S	L441P	R1283M	S912L
3849+40A-->G	E831X	G970D	L453S	R1283S	S945L
3850-3T-->G	E92K	H1054D	L619S	R170H	S977F
4005+2T-->C	F1016S	H1085P	L967S	R258G	T1036N
5T;TG12	F1052V	H1085R	L997F	R297Q	T1053I
5T;TG13	F1074L	H1375P	M1101K	R31C	T1086I
546insCTA	F1099L	H139R	M1137V	R31L	T1246I
621+3A-->G	F1107L	H199Y	M150K	R334L	T1299I
711+3A-->G	F191V	H620P	M152V	R334Q	T338I
A1006E	F200I	H620Q	M265R	R347H	T351I
A1067P	F311del	H939R	M952I	R347L	V1153E
A1067T	F311L	H939R;H949L	M952T	R347P	V1240G
A107G	F508C	I1027T	N1088D	R352Q	V1293G
A120T	F508C;S1251N	I105N	N1303I	R352W	V201M
A234D	F508del	I1139V	N1303K	R516S	V232D
A309D	F575Y	I125T	N186K	R553Q	V392G
A349V	F587I	I1269N	N187K	R555G	V456A
A455E	G1047R	I1366N	N418S	R668C	V456F
A46D	G1061R	I148N	P140S	R709Q	V562I
A554E	G1069R	I148T	P205S	R74Q	V603F
A62P	G1123R	I175V	P499A	R74W	V754M
C491R	G1244E	I331N	P574H	R74W;D1270N	W1098C
D110E	G1247R	I336K	P5L	R74W;V201M	W1282R
D110H	G1249R	I502T	P67L	R74W;V201M;D1270N	W361R
D1152H	G126D	I506L	P750L	R751L	Y1014C
D1270N	G1349D	I556V	Q1291R	R75L	Y1032C
D1445N	G178E	I601F	Q1313K	R75Q	Y109N
D192G	G178R	I618T	Q237E	R792G	Y161D
D443Y	G194R	I807M	Q237H	R933G	Y161S
D443Y;G576A;R668C	G194V	I980K	Q359R	S1045Y	Y301C
D565G	G27E	K1060T	Q372H	S108F	Y563N
D579G	G27R	K162E	Q493R	S1159F	
D614G	G314E	K464E	Q552P	S1159P	

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- No applicable codes

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POLICY HISTORY

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